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ROX index as a good predictor of high flow nasal cannula failure in COVID-19 patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis

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ABSTRACT

Purpose: Prediction of high flow nasal cannula (HFNC) failure in COVID-19 patients with acute hypoxemic respiratory failure (AHRF) may improve clinical management and stratification of patients for optimal treatment. We performed a systematic review and meta-analysis to determine performance of ROX index as a predictor of HFNC failure.

Materials and methods: Systematic search was performed in electronic databases (PubMed, Google Scholar, Web of Science and Cochrane Library) for articles published till 15 June 2021 investigating ROX index as a predictor for HFNC failure. Quality In Prognosis Studies (QUIPS) tool was used to analyze risk of bias for prognostic factors, by two independent authors.

Results: Eight retrospective or prospective cohort studies involving 1301 patients showed a good discriminatory value, summary area under the curve (sAUC) 0.81 (95% CI, 0.77–0.84) with sensitivity of 0.70 (95% CI, 0.59–0.80) and specificity of 0.79 (95% CI, 0.67–0.88) for predicting HFNC failure. The positive and negative likelihood ratio were 3.0 (95% CI, 2.2–5.3) and 0.37 (95% CI, 0.28–0.50) respectively, and was strongly associated with a promising predictive accuracy (Diagnostic odds ratio (DOR) 9, 95% CI, 5–16).

Conclusion: This meta-analysis suggests ROX index has good discriminating power for prediction of HFNC failure in COVID-19 patients with AHRF.

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1. Introduction

Coronavirus disease 2019 (COVID-19) has so far led to a huge disruption in socio-economic conditions and death of more than 3.8 million people worldwide [1]. Treatment of acute hypoxemic respiratory failure (AHRF) in COVID-19 patients is critical for saving lives. High flow nasal cannula (HFNC) oxygen therapy has now been successfully used as a non-invasive procedure in the management of AHRF in COVID-19 patients [2]. However, many patients have suffered from HFNC failure in the management of AHRF and lead to worsening of conditions [3].

Thus the early prediction of HFNC failure at the time of acute period of AHRF may improve clinical management and stratification of patients for optimal treatment. Recently some studies have evaluated prognostic

significance of Sequential Organ Failure Assessment (SOFA) score [4,5] and acute physiology and chronic health evaluation (APACHE II) score [4,6] for predicting HFNC failure.

The ROX index, a score that has been accepted in the management of pneumonia and acute respiratory distress syndrome (ARDS) [7,8], could have the potential to predict HFNC outcomes in COVID-19 patients.

Roca et al. were the first to use ROX index to predict HFNC failure in ICU patients suffering from pneumonia [8]. ROX index is described as a combination of the ratio of oxygen saturation to the fraction of inspired oxygen [SpO₂/FiO₂] and respiratory rate. The use of the ROX index could improve the management and treatment of patients with COVID-19 during the current pandemic and recently describe in a variety of observational studies. As it takes only a few data sets and is easy to measure at the bedside and may have great clinical utility.

Several studies during the COVID-19 pandemic have been reported to assess the predictive accuracy of the ROX index for predicting HFNC failure, but the findings are inconsistent due to differences in the clinical setting, cut-off used and heterogeneous population [4,7,9–14].

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Computing the pooled predictive power of the ROX index in predicting HFNC failure would provide key information for its evidence-based use in clinical settings. Therefore, we aimed to conduct a systemic review and meta-analysis to determine the predictive accuracy of the ROX index for predicting HFNC failure in COVID-19 patients with AHRF.

2. Materials and methods

The protocol for our systemic review was registered on PROSPERO (CRD42021236603). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) declaration [15] and the Cochrane Handbook for Systematic Reviews of Interventions [16] were used to carry out this study.

2.1. Study selection criteria

All citations were screened in duplicate, with any discrepancies settled through conversation and, if necessary, third-party arbitration. Two authors (JP, PKB) independently and repeatedly screened all possibly important citations and references in two phases, first reviewing titles and abstracts and thereafter complete manuscripts for those which qualified the parameters. Disagreements were settled by a third author (AK). We recorded the criteria for exclusion during the full manuscript review stage.

2.2. Types of studies

We included retrospective or prospective cohort studies to predict the HFNC failure in patients with COVID-19 with AHRF. Case reports, case series (describing only phenomenology without outcome ascertainment and those with sample size less than 10), review articles, abstract publications, and conference presentations were excluded.

2.3. Types of participants

We included COVID-19 patients (>18 years), diagnosed with reverse transcription-polymerase chain reaction (RT-PCR) testing, with AHRF who required HFNC in the hospital or intensive care unit (ICU). We accepted AHRF definition used by the study authors.

2.4. Exposure

ROX index score using any cut off value.

2.5. Comparison

HFNC success versus HFNC failure.

2.6. Types of outcome measures

HFNC failure, was defined as use of either invasive or non-invasive mechanical ventilation.

2.7. Search methods for identification of studies

We searched electronic databases such as PubMed, Google Scholar, Web of Science, and the Cochrane Library for articles published between the inception of the database and 15 June 2021. There was no language barrier; however, the filter was only applied to COVID-19 patients. We also checked the references of related journals to make sure we didn't skip any studies.

2.8. Data extraction and quality assessment

Data were extracted independently by two authors (JP and AK) using predefined data abstraction forms. We used two tier approach

to resolve conflicts between two authors performing data extraction; first through discussion between them; but if the issues remained unresolved we invited a third author (AKY) to do independent data extraction followed by discussion to resolve the conflict. The following data were abstracted: study characteristics, demographic data, outcomes, and individual study risk of bias. HFNC failure was described as patients who needed non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV) for the context of this research. The following data were collected for each eligible study: authors, publication year, country, study design, study group, proportion of HFNC failure, sensitivity, specificity, true positive, true negative and receiver operating characteristic (ROC) curve alongwith demographic and baseline characteristics such as sample size, a cut-off value of ROX, age, sex, body mass index (BMI), diabetes mellitus (DM), hypertension, lymphocyte count, CRP, D-dimer, length of HFNC, SOFA score, HFNC delivery device, humidifier, flow rate and FiO₂.

We used the Quality In Prognosis Studies (QUIPS) tool [17] to assess the risk of bias (RoB) independently and in duplicate in studies of prognostic factors. This tool summarizes the six bias domains, including prompting items and considerations for each one, as well as overall rating assessments. For each of the following domains, QUIPS tool classifies RoB as "low", "moderate" or "high": study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

2.9. Statistical analysis

This meta-analysis, which was carried on purpose to predict HFNC failure, included all patients who have been allocated to the current study. Data were obtained through direct extraction or indirect calculation. In our meta-analyses, DerSimonian and Laird random-effects model was used. The inverse variance approach was used to construct study weights. The Cochran Q test for heterogeneity and the I² statistic [18], were used to determine heterogeneity between studies. We also looked at the funnel plot visually to see if there was any publication bias.

We conducted meta-regression analyses to explore potential sources of heterogeneity among studies. We examined potential sources of heterogeneity keeping following variables as covariate/moderator variables; mean age (continuous variable), percent of hypertensive subjects (continuous variable), percent with diabetes (continuous variable), mean D-dimer level (continuous variable), percent of male gender (continuous variable), percent of cardiac disease (continuous variable), mean CRP (continuous variable) and time of ROX index (continuous variable), Cut-off value (continuous variable). Considering the clinical relevance, we further conducted a sub-group analysis for ROX index examined within 6 h/all studies and cut-off value of ROX index ≤5/ >5. We considered a normal distribution for continuous variables and converted interquartile ranges to standard deviations (SD) using Cochrane Collaboration guidelines [19]. Finally, the findings were depicted in forest plots. All the statistical analysis was conducted STATA version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3. Results

3.1. Search results and study characteristics

Initially, a total of 176 potentially eligible studies were identified. 54 full-text studies were extracted for screening after duplicate results were removed and titles and abstracts were screened. We contacted through e-mail the authors of relevant articles and we got data for our meta-analysis from two authors, however, five authors did not respond. Finally, eight retrospective or prospective cohort studies [4,7,9–14] including 1301 patients were considered for pooled analysis [Fig. 1] to determine the predictive accuracy of the ROX index for HFNC failure. Table 1 shows the study characteristics of each study included in the

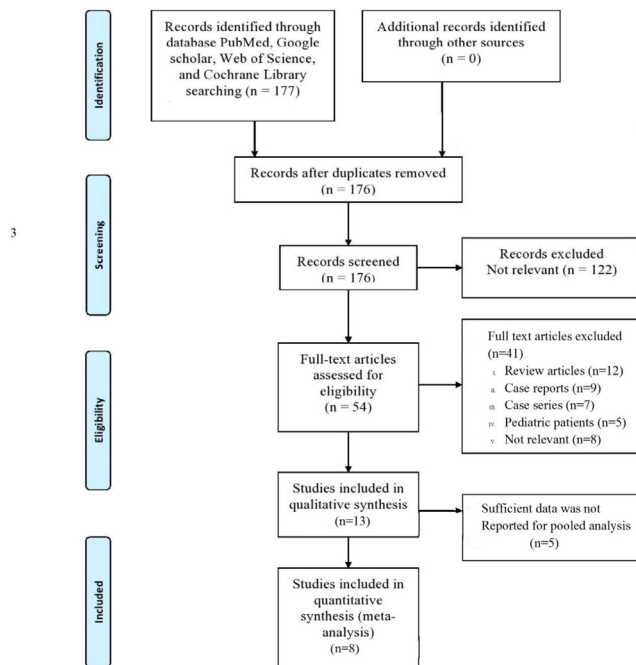


Fig. 1. PRISMA flow diagram.

present study. Table 2 show the demographic parameters and characteristics of the patients involved in the study. Five of the included studies had a low risk of bias [4,7,9,11,13], one trial had a high risk of bias [12], and two trials had a moderate risk of bias [10,14]. Five trials took place in the ICU setting [9–13] while three trials were conducted in the respiratory care unit [4,7,14]. The risk of bias in the individual study included in the present meta-analysis is shown in Fig. 2.

3.2. Outcomes

A total of eight studies involving 1301 subjects met the inclusion criteria of the present meta-analysis. We observed that the ROX index score show good discrimination with summary area under the curve (sAUC) of 0.81 (95% CI, 0.77–0.84) [Fig. 3]. The pooled sensitivity and

specificity were 0.70 (95% CI, 0.59–0.80) and 0.79 (95% CI, 0.67–0.88), respectively for predicting HNFNC failure in COVID-19 patients [Fig. 4]. Inconsistency measured by I^2 statistics were significant (86% for sensitivity and 85% for specificity) [Fig. 4]. The positive and negative likelihood ratio were 3.0 (95% CI, 2.2–5.3) and 0.37 (95% CI, 0.28–0.50) respectively, and had a substantially good diagnostic odds ratio (OR 9, 95% CI, 5–16) for predicting HNFNC failure outcome in COVID-19 patients [Fig. 5]. We did not observe the significant publication bias of the funnel plot ($P = 0.64$) suggesting the reliability of the study findings [Fig. 6]. Considering the pre-test probability of 50%, a ROX index may be linked with a positive likelihood ratio of 3.0 and a post-test HNFNC failure probability of 77%. The negative likelihood ratio was 0.37 associated with a post-test negative predictive value of 27%. We explored the source of heterogeneity using the clinically important variables (hypertension, diabetes, cardiac disease, mean age, gender, D-dimer, CRP, time of ROX index) on the effect size, however, we did not observe anyone the variables significantly explain the source of variation on pooled sensitivity and pooled specificity [Fig. 7].

Subgroup analysis: We conducted a subgroup analysis based on the timing of ROX- index assessment and cut-off value reported in the included studies. Our subgroup analysis did not observe the significant difference in the predictive accuracy of ROX-index including only those studies which examined ROX-index ≤ 6 h compared to overall studies. The sAUC was 0.81 (95% CI, 0.77 to 0.84) and 0.81 (95% CI 0.78 to 0.84) respectively. Similarly, eight studies reporting the predictive accuracy of ROX-index divided into cut-off value ≤ 5 (four studies) and > 5 (four studies). Our subgroup analysis demonstrated higher discriminatory accuracy including studies used cut-off value > 5 [sAUC, 0.87 (95% CI, 0.83 to 0.89)] compared to ≤ 5 cut-off value [sAUC, 0.76 (95% CI 0.72 to 0.80)], respectively with P value = 0.002 [Table 3].

4. Discussion

This systematic review and meta-analysis which included an extensive literature search, pre-registered protocol, a focus on only COVID-19 patients with AHRF, the use of the QUIPS tool to determine study bias, and the inclusion of recent trials suggests that ROX index is a good predictor of HFNC failure in COVID-19 patients with AHRF. Up to the best of our knowledge, this would be the first meta-analysis on ROX index for the prediction of HFNC outcomes in COVID-19 patients.

HFNC failure has been linked to a poor clinical outcome, predicting the failure of HFNC has remained a focus of research. In the clinical

Table 1
Basic characteristics of the included studies.

Study	Study type	Country	Settings	Patients	Delivery device	Humidifier	Flow rate (L/min)	FiO2
Chandel [9]	Multi-centered observational cohort study	USA	ICU	COVID-19	Fisher & Paykel Optiflow™ system	MR810 heated humidifier	N/a	N/a
Calligaro [11]	Multi-centered observational study	South Africa	ICU	COVID-19	Hamilton C1 Ventilator, AIRVO™ (Fisher & Paykel) or Inspire O ² FLO	N/a	50–60 L/min	0.8–1.0
Hu [4]	Retrospective observational study	China	Respiratory wards	COVID-19	AIRVO2, Fisher & Paykel	N/a	30 L/min	1.0
Panadero [14]	Retrospective observational study	Spain	Intermediate Respiratory Care Unit (IRCUC)	COVID-19	AIRVO2, Fisher & Paykel	N/a	50–60 L/min	N/a
Xu [13]	Multicenter retrospective observational study	China	ICU	COVID-19	Fisher & Paykel	N/a	30 L/min	N/a
Vega ML [7]	Retrospective observational study	Italy	Respiratory wards	COVID-19	N/a	N/a	50–60 L/min	N/a
Blez [12]	Prospective observational study	France	ICU	COVID-19	Optiflow®	MR810 heated humidified	60 L/min	1.0
Zucman [10]	Retrospective observational study	France	ICU	COVID-19	Fisher & Paykel	N/a	50 L/min	0.8

ICU: intensive care unit; COVID-19: coronavirus disease 2019; FiO2: fraction of inspired oxygen; N/a- not available.

Table 2
Demographic parameters and characteristics of the patients included in studies.

Study	HFNC status	Sample size	Cut-off value of ROX with time (h) after HFNC initiation	Age (Yr)	Sex (M/F)	BMI (kg/m ²)	DM	Hypertension	Lymphocyte count (10 ⁹ /L)	CRP (mg/L)	D-dimer (µg/ml)	SOFA Score	Length of HFNC (days)	AHRF
Chandel [9]	HFNC	164	3.67	54 ± 14	104/60	28.6 ± 5.7	56	64	N/a	16.7 ± 10.2	1.3 ± 1.6	2 ± 2.2	4 ± 3.7	SpO2 <88% RR > 35 breath/min
	Success	108	(at 12 h)	60 ± 13	76/32	28.7 ± 6.4	45	52		[IQR 9.8–23.6]	[IQR 0.8–2.2]	[IQR 1–4]	[IQR 2–7]	
	HFNC Failure									[IQR 10.8–26.3]	[IQR 0.9–2.7]	[IQR 2–7]	[IQR 1–4]	
Calligaro [11]	HFNC	134	2.7	50 ± 9.6	79/58	N/a	76	59	1.23 ± 0.6	173 ± 125.2	0.56 ± 1.5	N/a	N/a	SpO2 <92% RR > 30 breath/min O2 supply– 15L/min
	Success	145	(at 6 h)	53 ± 10.4	84/72	82	72	[IQR 0.83–1.62]	[IQR 105–274]	[IQR 0.36–1.78]	N/a	N/a		
	HFNC Failure							1.15 ± 0.5	235 ± 149.6	1.03 ± 4.1				
Hu [4]	HFNC	65	5.55	59.5 ± 10.9	26/39	N/a	N/a	N/a	0.62 ± 0.2	45.6 ± 39.3	0.62 ± 1.5	3 ± 0	6 ± 3.7	SpO2≤92% RR ≥25 breath/min
	Success	40	(at 6 h)	71.3 ± 7.6	25/15	0.7 ± 0.30	39.3 ± 45.9	1.04 ± 4.7	4 ± 1.5	3 ± 6.7				
	HFNC Failure										[IQR 0.49–0.79]	[IQR 30.4–83.5]	[IQR 0.42–1.78]	
Panadero [14]	HFNC	19	4.94	56.6 ± 12.8	14/5	28.1 ± 3.2	3	9	0.62 ± 0.2	45.6 ± 39.3	0.62 ± 1.5	3 ± 0	6 ± 3.7	SpO2≤92% RR ≥25 breath/min
	Success	21	(2 to 6 h)	60.9 ± 10.8	14/7	30.5 ± 5.1	5	7	N/a	1283 ± 1006	6.2 ± 14.4	4.5 ± 0.8	6 ± 2.22	
	HFNC Failure													
Xu [13]	HFNC	173	5.31	60.6 ± 15.5	119/58	N/a	34	78	0.6 ± 0.37	N/a	2.6 ± 5.9	2.0 ± 1.1	10 ± 5.9	SpO2 <90% RR> 30 breath/min O2 supply– 10L/min
	Success	220	(within 4 h)	66.3 ± 12.5	100/47	26	69	0.6 ± 0.3	N/a	4.8 ± 16.9	4 ± 1.5	3 ± 2.2		
	HFNC Failure												[IQR 0.4–0.9]	
Vega [7]	HFNC	85	5.99	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
	Success	35	(at 12 h)	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a		
	HFNC Failure												[IQR 0.4–0.8]	
Blez [12]	HFNC	14	4.88	64 ± 11.1	11/3	25.6 ± 2.6	2	6	N/a	N/a	N/a	N/a	N/a	RR≥ 30 breath/min O2 supply– 10L/min
	Success	16	(at 0.5 h)	64 ± 5.4	10/6	30.5 ± 3.5	5	10	N/a	N/a	N/a	N/a		
	HFNC Failure												[IQR 57.5–72.5]	
Zucman [10]	HFNC	21	5.37	55 ± 11.11 [IQR 48–63]	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
	Success	41	(within 4 h)											

HFNC, high-flow nasal cannula; BMI: body mass index; DM: diabetes mellitus; CRP: C-reactive protein; SOFA: sequential organ failure assessment; AHRF– acute hypoxemic respiratory failure, RR– respiratory rate, IQR– interquartile range, N/a– not available, Yr– year.



Fig. 2. Risk of bias summary.

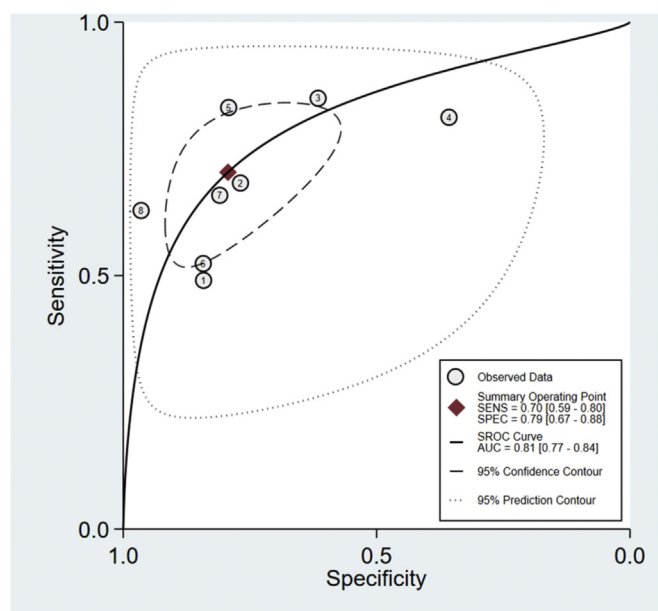


Fig. 3. Summary receiver operating characteristic graph for the included studies. The AUC of ROX-index for probability in predicting HFNC failure was 0.81 (95% CI, 0.77–0.84).

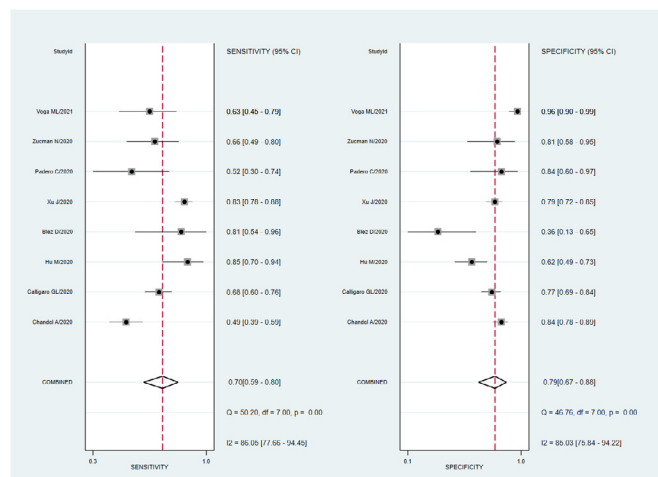


Fig. 4. Forest plot of the sensitivity and specificity of ROX-index for predicting HFNC failure in patients with COVID-19. The pooled sensitivity and specificity were 0.70 (95% CI, 0.59–0.80) and 0.79 (95% CI, 0.67–0.88), respectively.

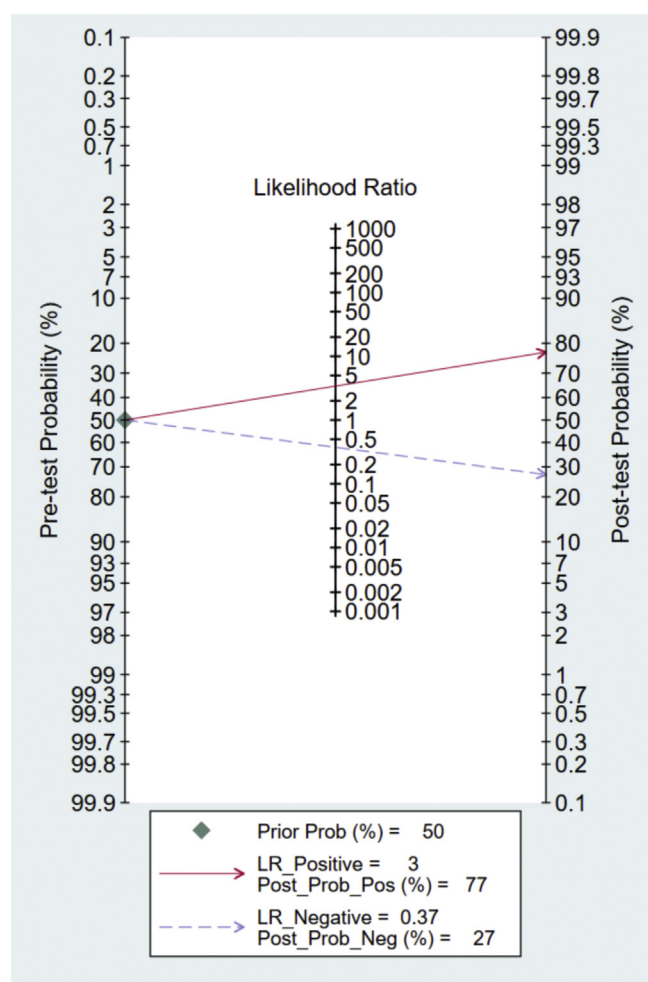


Fig. 5. Fagan nomogram showing pre-test probability and post-test probability using ROX index for predicting HFNC failure.

practice of treating AHRF in patients with COVID-19, studies have observed that the ROX index has a good predictive value in HFNC failure. Studies have reported various thresholds to ROX for predicting HFNC outcomes. Clinicians are therefore unclear regarding the optimal thresholds of ROX that should be applied to know the HFNC outcomes.

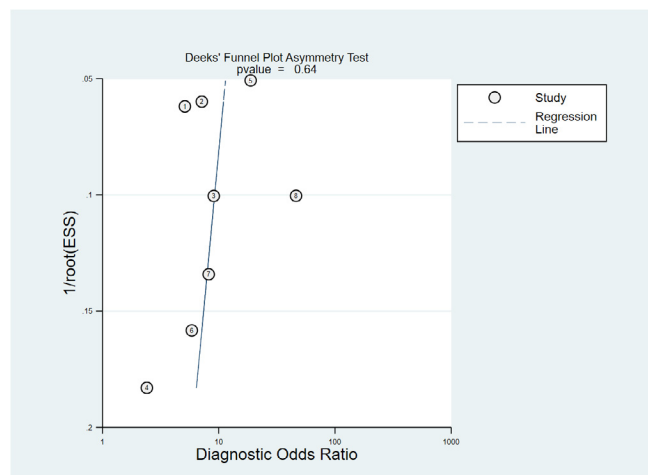


Fig. 6. Deek funnel plot showing publication bias for studies included in the meta-analysis.

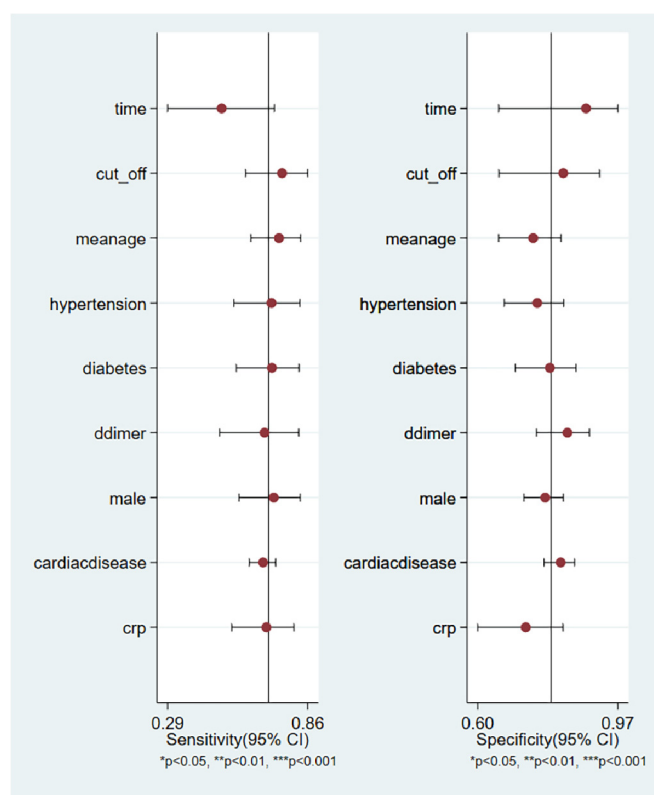


Fig. 7. Forest plot showing pooled sensitivity and pooled specificity of clinical variables for predicting HFNC Failure.

Previous data from AHRF patients treated with HFNC revealed that the set flow rate has a significant impact on oxygenation and RR; it was then investigated whether increasing the set flow rate would affect the ROX index.

In the current meta-analysis, we observed that the ROX index could be used for risk stratification in determining whether or not a patient requires mechanical ventilation at an early hour of admission. It was demonstrated that the ROX index is a convenient tool that can distinguish patients with COVID-19 infection who need hospitalization (ROX index less than 25.7) from those who can be safely discharged at the time of admission. Also, in COVID-19 patients with AHRF, the ROX index has high sensitivity, confirming that a lower ROX index predicts higher mortality risk [20]. Our meta-analysis showed that ROX index might discriminate with a value of sAUC of 0.81 (95% CI, 0.77–0.84) with sensitivity of 0.70 (95% CI, 0.59–0.80) and specificity of 0.79 (95% CI, 0.67–0.88) for predicting HFNC failure in COVID-19 patients. The heterogeneity (I^2 or inconsistency) was significant (86% for sensitivity and 85%, for specificity). We explored

the source of factors that may influence variation in the studies using meta-regression analysis, although the potential clinical conditions e.g. proportion of hypertension, the proportion of diabetes, mean age, D-dimer level, the proportion of male subjects, presence of cardiac disease, CRP level, and lymphocyte count did not influence the pooled prognostic value of ROX-index for prediction of worse outcome except lymphocyte count for specificity which was significant. The absence of publication bias further confirms the validity of the findings observed in the current meta-analysis.

The cut-off value used in the included studies varied from 2.7 to 5.9 in obtaining the homogenous and clinically acceptable cut-off value. We excluded the extreme outlier cut-off value of 25.26 in the paper published by Suliman et al. [21]. Based on the studies included in the meta-analysis, the optimal cut-off value may fall close to 5 of ROX index within the 24 h of admission for predicting HFNC failure.

Timing of the measurement of ROX index among the included studies ranged from 2 h to 12 h. Only two studies reported data for prognostic accuracy of ROX index at 12 h. Our meta-regression analysis did not observe significant moderator effect of differences in the timing of ROX index examination on discriminatory power of ROX index. Still we conducted a subgroup analysis also, and observed that discriminatory ability of ROX index based on studies that examined ROX-index within 6 h which was comparable to finding when all studies were included in the analysis. Early prediction of outcome is needed to provide optimal care to patients and stratification at the earliest hours to predict HFNC failure. A study published by Lemiale et al. [22] also observed that maximum diagnostic accuracy and static measurement of the ROX index was at 6 h.

The finding of the present study indicate that the ROX index could help in identifying subjects at more risk for worse outcomes therefore, early invasive mechanical ventilation may be used to prevent worse outcomes in patients with COVID-19-associated AHRF.

4.1. Limitations

The limitations of our study were that none of the studies included in the meta-analysis have shown the calibration and validation of the model which limits the validity of the prediction accuracy of the ROX index. We also observe high heterogeneity among the studies as indicated by I^2 , indicating the need to conduct well-designed prospective studies. The cut-off value for the ROX index was not uniform across the studies included in the meta-analysis which may be due to different clinical conditions of patients and settings. However to obtain the uniform results we have excluded the studies used extreme cut-off value. We were also not able to obtain data from five studies which could have decreased the power of the study. Meta-regression analysis does not have adequate power due to limited number of studies to examine the sources of heterogeneity.

Table 3
Results of subgroup analysis using ROX index for predicting HFNC failure.

Categories	Sensitivity (95% CI)	Specificity (95% CI)	sAUC (95% CI)	DOR (95% CI)	I^2
Time from onset to ROX- index assessment					
All studies	0.70 (0.59 – 0.80)	0.79 (0.67 – 0.88)	0.81 (0.77 – 0.84)	9 (5 – 16)	Sensitivity: 86.05% Specificity: 85.03%
Within 6 h	76 (0.65 – 0.84)	0.74 (0.62 – 0.83)	0.81 (0.78 – 0.84)	9 (5 – 15)	Sensitivity: 77.15% Specificity: 75.79%
Cut-off value					
Cut-off ≤ 5	0.65 (0.48 – 0.79)	0.75 (0.59 – 0.87)	0.76 (0.72 – 0.80)	6 (4 – 9)	Sensitivity: 77.01% Specificity: 84.38%
Cut-off > 5	0.77 (0.65 – 0.86)	0.85 (0.67 – 0.94)	0.87 (0.83 – 0.89)	19 (11 – 35)	Sensitivity: 76.53% Specificity: 89.15%

sAUC – summary area under the curve, DOR- diagnostic odds ratio, CI- confidence interval.

5. Conclusion

Our meta-analysis demonstrated that the ROX index has good discriminating power for the prediction of HFNC failure in COVID-19 patients with AHRF. Further large-scale, multicenter studies with uniform cut-offs and at specific time intervals are needed to strengthen the current findings.

Conflicts of interest

NIL

Funding

NIL

Author's statements

Jay Prakash developed the initial idea of this study and conducted a comprehensive search of four databases. Jay Prakash and Pradip Kumar Bhattacharya took responsibility for selecting the study. Jay Prakash, Amit Kumar and Arun Kumar Yadav extracted data. All authors have made their contributions to research design, interpretation of results, and ideas for writing articles. Jay Prakash and Amit Kumar synthesized and analyzed the data and drafted the article. Kameshwar Prasad, Arun Kumar Yadav and Lal Chand Tudu reviewed this article and provided suggestion for it. All of the authors have carefully examined this manuscript and agreed with the ideas presented in the article.

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